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TECH CENTER: 1300/2000
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period of response be extended three months up to and including April 26, 2001. A fee for the three-month extension of time of \$890.00 is provided herewith.

IN THE SPECIFICATION

Replace the paragraph beginning on page 16, line 28, and ending on page 18, line 3, with the following paragraph:

--There are many known ways to construct adenovirus vectors. As discussed above, one of the most commonly employed methods is the so called "two plasmid" technique. In that procedure, two noninfectious bacterial plasmids are constructed with the following properties: each plasmid alone is incapable of generating infectious virus. However, in combination, the plasmids potentially can generate infectious virus, provided the viral sequences contained therein are homologously recombined to constitute a complete infectious virus DNA. According to that method, typically one plasmid is large (approximately 30,000-35,000 nt) and contains most of the viral genome, save for some DNA segment (such as that comprising the packaging signal, or encoding an essential gene) whose deletion renders the plasmid incapable of producing infectious virus. The second plasmid is typically smaller (eg 5000-10,000 nt), as small size aids in the manipulation of the plasmid DNA by recombinant DNA techniques. Said second plasmid contains viral DNA sequences that partially overlap with sequences present in the larger plasmid. Together with the viral sequences of the larger plasmid, the sequences of the second plasmid can potentially constitute an infectious viral DNA. Cotransfection of a host cell with the two plasmids produces an infectious virus as a result of homologous recombination between the overlapping viral DNA sequences common to the two plasmids. One particular system in general use by those skilled in the art is based on a series of large plasmids. One particular system in general use by those skilled in the art is based on a series of large plasmids known as pBHG10, pBHG11 and pBHG13 described by Bett, A. J., Haddara, W., Prevec, L. and Graham, F.L: "An efficient and flexible system for construction of adenovirus vectors with insertions or deletions in early regions 1 and 3," Proc. Natl. Acad. Sci. US 91: 8802-8806, 1994 and in US patent application S/N 08/250,885, now issued as U.S. Patent No. 6,140,087, and published

as WO95/00655 (hereby incorporated by reference). Those plasmids contain most of the viral genome and are capable of producing infectious virus but for the deletion of the packaging signal located at the left end of the wild-type viral genome. The second component of that system comprises a series of "shuttle" plasmids that contain the left approximately 340 nt of the Ad genome including the packaging signal, optionally a polycloning site, or optionally an expression cassette, followed by viral sequences from near the right end of E1 to approximately 15 mu or optionally to a point further rightward in the genome. The viral sequences rightward of E1 overlap with sequences in the pBHG plasmids and, via homologous recombination in cotransfected host cells, produce infectious virus. The resulting viruses contain the packaging signal derived from the shuttle plasmid, as well as any sequences, such as a foreign DNA inserted into the polycloning site or expression cassette located in the shuttle plasmid between the packaging signal and the overlap sequences. Because neither plasmid alone has the capability to produce replicating virus, infectious viral vector progeny can only arise as a result of recombination within the cotransfected host cell. Site-specific methods for achieving recombination may also be employed when practising the present invention.--

IN THE CLAIMS

Claim 13 (Amended):

- 1 13. A method of making a series of genetically identical adenoviral vectors wherein each member
- 2 of said series has a different serotype, for delivering and expressing a desirable gene in a recipient
- 3 of said series of genetically identical adenoviral vectors which comprises:
- 4 (a) making a series of helper adenoviruses of differing serotypes, each serotype of said series of
- 5 adenoviruses expressing a different set of capsid proteins;
- 6 (b) making a helper dependent adenovirus vector, hdAd, having a genome encoding said gene, an
- 7 adenoviral packaging signal, the adenoviral left ITR and the adenoviral right ITR and as much
- 8 additional nucleic acid sequences as are necessary to ensure expression of said gene and packaging
- 9 of said hdAd genome, but encoding little or no adenoviral gene products;
- 10 (c) generating a first stock of said hdAd *in vitro* by co-introducing into a cell said hdAd genome and